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ABSTRACT

This introduction to the Marfan syndrome, a heritable disorder of connective tissue primarily affecting the bones and ligaments, eyes, cardiovascular system, and lungs, is intended for a general audience. The question-and-answer format was chosen by individuals with the syndrome to reflect their major questions and concerns. It incorporates the experiences of patients, relatives, and health professionals. Topics addressed include: skeletal features; effects on the eyes; cardiovascular features; other features; causes; diagnosis; who can be affected; potential for a cure; the most effective forms of treatment; the outlook and lifestyle for affected persons; common parent reactions; common reactions of affected adults; reactions of teenagers and young adults; family concerns; use of medications or special diets; how the syndrome is passed in families; the decision of affected persons to have children; need for informed physicians in routine medical care; current research; and organizations providing support and information. (MSE)

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The Marfan Syndrome

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The **Marfan** Syndrome

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National **Marfan** *Foundation*
NEW YORK

"We thank all those who commented on the first edition of this booklet. Many suggested improvements have been incorporated. Joan Weiss and Barbara Bernhardt contributed important ideas to this revised effort."

Reed Pyeritz, M.D.,Ph.D

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Introduction

This brochure is intended for anyone interested in learning more about the Marfan syndrome. The format was selected by persons affected by this condition to reflect their major questions and concerns. The vocabulary has been chosen to avoid medical jargon, although words and phrases that one might encounter in conversations with physicians, in their reports, or in the medical literature are noted parenthetically. The experience of a large number of patients, relatives and health professionals has been distilled into this brochure. Every effort has been made to minimize biases and speculation. Nonetheless, differences of opinion on many of the points discussed may arise, and the editors encourage correspondence from all who wish to make the next edition of this brochure even better.

What is the Marfan syndrome?

The Marfan syndrome is a medical condition, classified as a heritable disorder of connective tissue, that primarily affects the bones and ligaments (the skeletal system), the eyes (the ocular system), the heart and blood vessels (the cardiovascular system) and the lungs. It is named after a French pediatrician, Antoine Marfan, who described in 1896 a 5-year-old girl whose limbs, fingers and toes were long and thin, whose muscle development was poor, and whose spine was curved abnormally. Subsequent physicians described other patients who, in addition to similar skeletal changes, also had abnormalities in different parts of their bodies. As a form of medical shorthand, Marfan's name became commonly used to refer to individuals who were, or were thought to be, affected by this condition. The term "syndrome" refers to the fact that this group of physical signs or changes occur together often enough for physicians to recognize a pattern. As will be discussed in this brochure, it is this pattern that is so important in understanding the nature and causes of a syndrome, in predicting the course of affected individuals and in devising forms of treatment.

There are over 100 different heritable disorders of connective tissue, including a few which closely resemble the Marfan syndrome. They are termed "heritable" because all have their basis in a genetic error (mutation) and, because relatives have genes in common, these conditions may affect more than one person in a family. Connective tissue can be viewed as the support tissue of the organs and of the body in general. Certain connective tissue components act as glue, others as scaffolding, and others permit elastic expansion and contraction.

What Are the Skeletal Features?

Bones and ligaments are affected in many and diverse ways. An affected individual will often be tall, slender and somewhat loose-jointed or limber. The arms, legs and fingers may be disproportionately long when compared with the trunk. Limberness extends to the feet where the arch is often flat. Spinal curvature is common and may become quite severe without treatment. The breast bone may either protrude (commonly called a pigeon breast; the medical term is pectus carinatum) or indent (funnel chest or pectus excavatum) due to the overgrowth of the ribs. The roof of the mouth (palate) is usually highly arched and the teeth are crowded. The face may appear long and narrow, in keeping with the general body shape. Infants often have deeply set eyes and appear older, or at least wiser, than their unaffected brothers or sisters were at the same age.

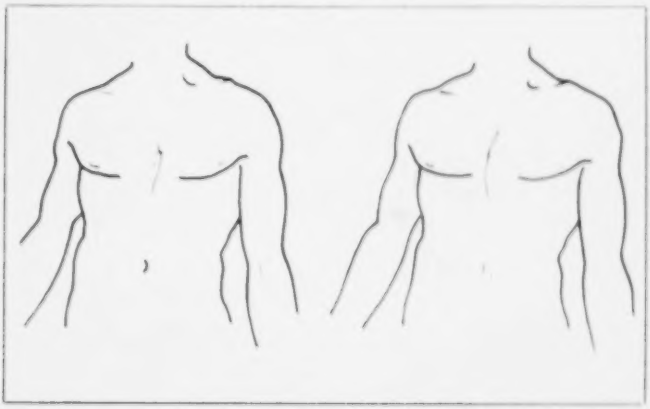

Figure 1. On the left is a funnel chest deformity (pectus excavatum) and on the right is a pigeon breast deformity (pectus carinatum).

How Are the Eyes Affected?

The lens of the eye is off-center or dislocated (ectopia lentis) in about 50% of persons with Marfan syndrome. The lens may be markedly off-center or be so subtly dislocated that an ophthalmologist might fail to detect the dislocation unless the pupils were fully dilated with eye drops. Dislocation of the lens occurs in relatively few other conditions, and is, therefore, an important hallmark of the Marfan syndrome when present. But the most common effect on the eye is nearsightedness (myopia). Again, the visual impairment might be mild or quite severe, and is independent of whether the lens is dislocated. Holes

or tears in the inner lining of the eye (retinal detachments) occur infrequently; persons who have had their lenses removed surgically seem to be more prone to problems with tearing of the retina.

Figure 2. Right eye of a person with dislocation of the lens; the lens is shifted up and to the side slightly.

What Features Are Present in the Cardiovascular System?

The heart and blood vessels are affected in nearly all persons, young or old, affected by the Marfan syndrome. First, the valves of the heart, those fine tissue leaflets that keep the blood flowing in the proper direction, are of abnormal composition and size in many instances.

In particular, the two *mitral valve* leaflets are too large for the opening they need to cover; the result is that the leaflets billow backward when the pumping chamber of the heart (left ventricle) contracts. This abnormal motion is called mitral valve prolapse and occurs in 75-85% of persons affected by the Marfan syndrome. Occasionally, prolapse can only be detected by a test, called an echocardiogram, in which high-frequency sound waves (ultrasound) are bounced off the heart to produce a sonar picture of how the valves move. In most people with a prolapse, the mitral valve makes a "click" as it moves backward, a sound heard through the stethescope. In most people with prolapse, the mitral valve does not leak. In about one-third, however, blood leaks "backward" through the valve and creates a heart murmur of a particular type, also easily detected by the physician. For many people with a leaking mitral valve (mitral valve regurgitation), no symptoms develop and the heart compensates quite well; if the leak remains small, minimal therapy is necessary. About 10% of individuals with mitral regurgitation in the Marfan symdrome do have progression of the problem and develop symptoms, such as

breathlessness on exercise or even at rest, a rapid or irregular pulse (palpitations), or extreme tiredness.

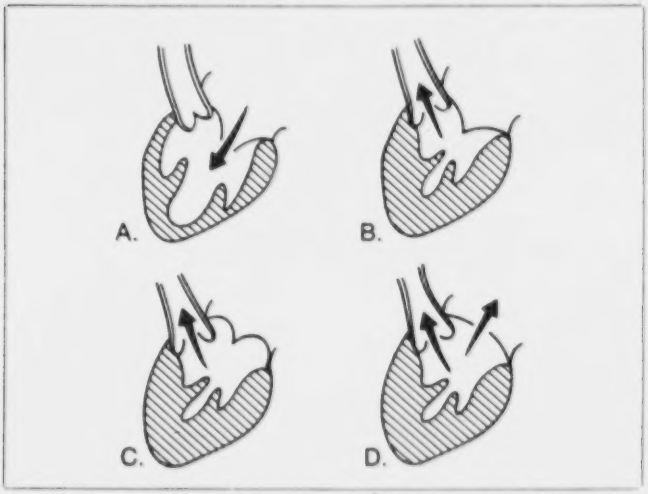

Figure 3. Normal and abnormal function of the mitral valve.

Fig. A. The left ventricle is in the resting phase (diastole) of the cardiac cycle. The mitral valve is open (arrow) and the blood is flowing from the lungs into the left ventricle.

Fig. B. The muscle of the left ventricle is contracting during the pumping phase (systole) and blood is flowing through the aortic valve (arrow) into the aorta. The mitral valve is closed in the normal position.

Fig. C. When mitral valve prolapse is present in mild form, the mitral valve billows backward but does not leak during systole. The arrow indicates the direction of blood flow.

Fig. D. When mitral regurgitation (often due to severe mitral valve prolapse) is present, blood leaks backward through the mitral valve which has not properly closed. The arrows indicate the direction of blood flow.

The heart muscle itself and the blood vessels that supply the heart muscle with blood (coronary arteries) rarely develop problems directly related to the Marfan syndrome, although the muscle may suffer damage as a result of valve leakage. On the other hand, persons with the Marfan syndrome have the same risk as anyone else for developing hardening of the arteries (atherosclerosis) and high blood pressure, disorders that also lead to heart disease.

Blood vessels include arteries, veins and the small capillaries in between. In the Marfan syndrome, primarily the largest artery, the *aorta*, is affected. The aorta arises directly from the outlet of the left ventricle; all blood

pumped from the heart must first pass into this artery. After leaving the heart, the aorta branches into large vessels that carry oxygen-rich blood to the entire body. A valve, the *aortic valve*, lies between the left ventricle and the aorta and functions to keep blood, once pumped out to the aorta, from leaking back to the heart.

The wall of the aorta consists of three parts: A thin, inner layer (intima), a thick, elastic middle layer (media), and an outer layer (adventitia). In the Marfan syndrome, the media is weaker than normal. Year after year, as the aortic wall faces the constantly changing stress generated by the beating heart, the wall, particularly the first two-to-four inches above the aortic valve (sinuses of Valsalva), gradually

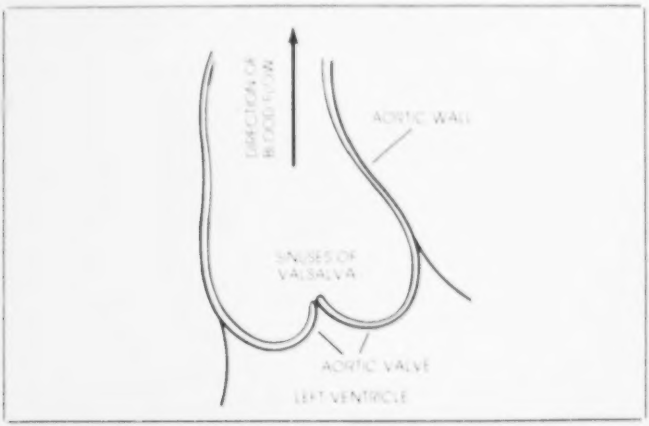

Figure 4. The aorta in cross-section. In an adult, the diameter in the region of the sinuses of Valsalva is, on average, 1-1.5 inches. The arrow shows the normal direction of blood flow during systole.

stretches. In this region, the diameter of the aorta, usually about one and one-half inches in an adult, widens (dilates); when the enlargement attains an arbitrary size (perhaps about three inches) physicians often refer to the dilated region as an aneurysm. As the aorta widens, two things can happen. First, the aortic valve leaflets are stretched and fail to completely close the aorta. This means that between heart beats, blood leaks back into the heart, causing the left ventricle to work harder to pump blood. Without treatment, the heart can become seriously overworked and reach a stage called heart failure. At this stage, the individual may have the same symptoms as someone with severe mitral regurgitation and, in addition, develop chest pain or fainting.

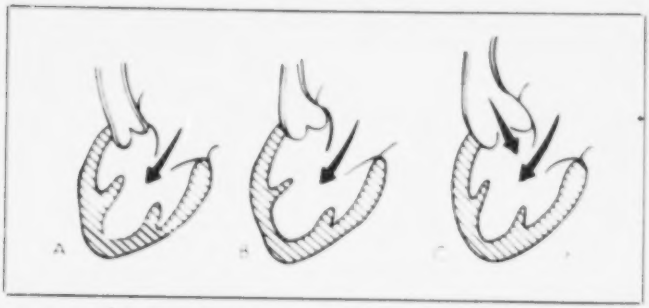

Figure 5. Aortic dilatation. In figure A, the heart is in diastole and the aortic valve is closed, preventing blood which has just been pumped into the aorta from leaking backward into the left ventricle. The aorta is not dilated. In Figure B, the aorta is moderately dilated, but the aortic valve still completely closes the opening. In Figure C, the aorta is greatly dilated and the aortic valve can no longer cover the opening; the result is leakage of blood back into the left ventricle, a condition called aortic regurgitation.

Second, as the aorta widens, a tear can develop in the inner wall and rapidly extend into the weak middle layer. Once the tear develops, the force of pumping blood can cause the middle layer to separate, forming an abnormal second channel through which blood can flow. This process is called a *dissection* and may be associated with severe chest and/or back pain or fainting. Eventually, at the leading edge of the abnormal channel, a second tear usually occurs, either inward, allowing blood to re-enter the aorta, or outward, producing a rupture with bleeding into the chest.

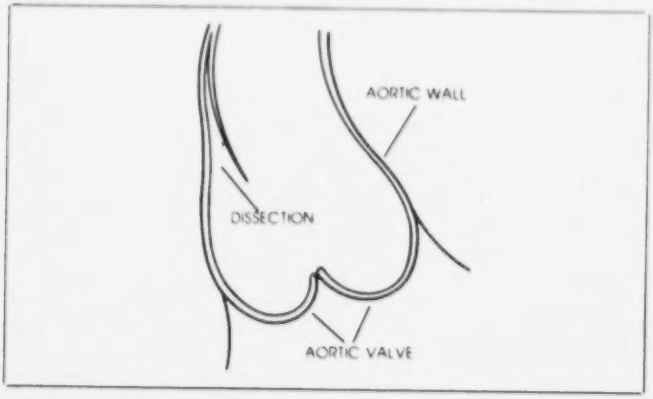

Figure 6. Aortic dissection. Most tears in the aortic wall occur just above the aortic valve in the Marfan syndrome.

The beginning portion of the aorta enlarges to some degree in nearly everyone with the Marfan syndrome. The echocardiogram is the simplest method for detecting and measuring the aorta in this region. This enlargement usually begins quite early in life, and is detectable using echocardiography in most infants with Marfan syndrome. In years past, most affected persons suffered one of the serious aortic complications. As will be discussed below, treatment methods are available which will head off these problems before major complications occur.

Are There Other Features of the Marfan Syndrome?

Stretch marks in the skin (striae distenseae) may occur in anyone, particularly as a result of pregnancy or marked weight gain and loss. Persons with the Marfan syndrome are prone to develop striae, often at an early age and without weight change. The striae tend to appear in sites subject to stress, such as the sholders, hips and lower back. Although some people find striae of cosmetic concern, they pose no risk and warrant no treatment, which is fortunate, because there is no effective means of preventing or removing them!

The lungs can be affected in several ways. Connective tissue is important in providing stability and elasticity to the tiny air sacs in the lungs. Nearly everyone with the Marfan syndrome has diminished elasticity when compared with persons of their own sex, age, build and smoking history. This rarely causes any noticeable problem, however. Marfan people are no more susceptible than others to lung disorders like asthma, pneumonia or bronchitis than the general population, but some evidence suggests an increased susceptibility to emphysema. A few people with the Marfan syndrome develop lung changes of emphysema even without being cigarette smokers. Spontaneous collapse of a lung (pneumothorax) occurs in about one person out of 20, or about 50 times the rate in the general population. This may occur out of the blue or after a minor blow to the chest. The symptoms are a feeling of breathlessness and often chest pain, which may be sharp or dull and may change with breathing in and out. This is always a problem that requires prompt attention but is rarely life-threatening.

What Causes the Marfan Syndrome?

Cause must be considered on several levels. The most correct and straight-forward answer is to state that a single abnormal (mutant) gene causes the condition. A gene is the

fundamental unit of heredity: humans have 50-100 thousand of them, each composed of DNA and organized along the chromosomes. Most genes occur in pairs. One member of each pair is inherited from the mother and one from the father. In anyone affected by the Marfan syndrome, the Marfan gene may be either inherited from a parent affected by the condition or from an unaffected parent who has had a change (mutation) in his sperm or her egg.

When most physicians think of cause, however, they are interested in what the mutant Marfan gene does, or does not do, to produce the syndrome. Here the answer is not yet clear. Most researchers believe that the Marfan gene produces a change in one of the proteins that provide strength to connective tissue, a protein such as collagen. Because connective tissue is so complex (there are at least five different forms of collagen) and such a wide variety of steps in connective tissue development could be disturbed and lead to the Marfan syndrome, discovering the so-called basic biochemical defect has been elusive. It is for this reason that, at this time, a physician cannot perform a laboratory test to confirm the diagnosis.

How is the Marfan Syndrome Diagnosed?

Because of the lack of a specific laboratory test at this time, the diagnosis must be based on the end result—the features present in the individual. However, the Marfan syndrome is typical of many heritable conditions in that the number and severity of the features are considerable, something called "variability" by geneticists. This means that some people will have only a few features while others will have many. Because most features progress with age, the diagnosis is often more obvious in older persons. But children, even newborns, can and should be examined. For these reasons, the diagnostic evaluation should be performed by physicians experienced with the condition. The evaluation should include:

1. A detailed medical and family history;
2. A complete physical examination;
3. A thorough eye examination by an ophthalmologist, who uses a slit lamp to look for lens dislocation after fully dilating the pupil;
4. A chest X-ray, looking for cysts in the lungs, enlargment of the heart and aorta, and curvature of the spine;
5. An EKG and an echocardiogram, looking for involvement of the cardiovascular system that is often not evident from the physical examination.

This series of steps is important, not only in determining the diagnosis, but in detecting the problems that require immediate or long-term management.

Who Can Be Affected?

Men and women of any race or ethnic group can be affected, and no group seems particularly susceptible. The Marfan syndrome is more common than textbooks or most physicians would lead one to believe, but even at a revised estimate of one person out of each 10,000 in the United States, it is not a common condition. Viewed another way, however, there are over 20,000 persons affected in this country alone. The Marfan syndrome is thus one of the more common heritable disorders, being more common than cystic fibrosis and hemophilia, and about as common in the United States as sickle cell disease.

Is a Cure Available?

At this time, a person cannot be cured of the Marfan syndrome, no matter how early in life the condition is diagnosed or how mild the symptoms are. A true cure would involve altering the gene responsible for the condition. Such genetic manipulation is gradually becoming feasible technically, but, as noted above, the gene responsible for the Marfan syndrome has not been isolated, and may be different from one family to the next. This is not to say, however, that effective treatment is unavailable.

What Forms of Treatment Are Most Effective?

Management and treatment of the Marfan syndrome is best discussed and understood by dealing with body systems. This is as true for physicians as it is for patients and relatives, which is why a number of medical specialists may become involved in the care of an affected person.

In the *skeletal system*, curvature of the spine and deformity of the chest represent the most serious problems. Either can be disfiguring or impair the function of the heart and lungs. With respect to the spine (vertebral column), the first step in mangement is routine evaluation on an annual basis by a physician who understands the potential problems. If abnormal spinal curvature is noted, X-rays are useful for measuring the angle of the curve. Abnormal curves tend to worsen during times of growth, particularly around puberty. Once a curve of more than about 10 degrees is observed, an orthopaedic surgeon who specializes

in backs should become involved in management. A removable brace is often effective in stabilizing the spine until growth is completed. If bracing is ineffective and the curve or curves worsen much beyond 35-40 degrees, various surgical procedures provide quite safe and satisfactory results, often with a return toward a normal shape. Because surgery does involve discomfort and wearing a body cast for months, it is reserved as a last resort. Careful follow-up greatly reduces the likelihood of an operation. Some children have been treated with hormones to advance the age at which puberty begins in order to "speed-up" the growth cycle and reduce the number of years during which the spine may deform. This treatment has been most effective in girls. Although medical side-effects are minimal, adult height is reduced by this treatment (a desireable side-effect to many parents!) and the child must deal with the social and psychologic trials of becoming sexually mature before his or her peers.

Both a funnel chest and a pigeon breast deformity can be corrected surgically. Because the deformity results from overgrowth of the ribs, however, the breast bone may be again pushed in or out if the surgery is done before the ribs stop growing. For this reason, repair of a chest deformity for cosmetic reasons is best delayed until mid-adolescence at the earliest. Occasionally, if the heart or lung are being severely compressed, the repair must be done during childhood.

Other skeletal problems rarely require extensive treatment. Fallen arches and long, narrow feet require careful attention to obtaining shoes that fit well. Looseness of joints may delay walking in infancy or lead to dislocations of joints, particularly the knee cap (patella). Usually, as a child ages, the joints develop more stability and the surrounding muscles develop enough strength to minimize these problems.

The narrowness of the roof of the mouth and relative smallness of the jaw produce crowding of the teeth. Any child with the Marfan syndrome needs good dental care and evaluation with early referral to an orthodontist if malalignment or malocclusion develop.

The *eyes* require careful attention from early in childhood. Failure to detect any of the several abnormalities that can affect vision may result in an imbalance in the two eyes (amblyopia) which becomes progressively more difficult to correct. In most persons, dislocation of the lens is a minor problem. Sometimes, the lens will actually interfere with vision. Special eyeglasses may be needed. Rarely, the lens may have to be removed, although this surgery is necessary far less often than was once believed. Because of an increased risk of retinal detachments, the eyes should be

protected from injury during work and sports. Activities that involve blows to the head, such as football, boxing and diving, should be avoided.

The *cardiovasular system* appropriately attracts much of the patient and physician interest regarding mangement. Here, too, the first line of defense is the routine evaluation. Only through regular check-ups and echocardiograms can function and size of the heart and aorta be assessed before serious problems arise. The risk of waiting until some symptom appears is great. For someone with no serious cardiovascular problem, an annual evaluation is adequate. Detection of significant heart murmurs or aortic enlargement may dictate more frequent visits. Occasionally, irregularities of the heart beat will require treatment with medication.

Failure of one of the heart valves to function properly can first be treated with various medications. If the function deteriorates further, surgical replacement with an artificial (prosthetic) valve becomes necessary. If the aortic valve is leaking, the aorta just above is nearly always markedly enlarged; current surgical therapy dictates replacing both the valve and several inches of aorta with a composite graft—a prosthetic valve sutured into one end of a woven cloth tube. Results with this method have been so successful that some physicians now recommend that certain patients have aortic surgery to prevent any sudden deterioration from occurring. Experience with this technique is growing across the United States and around the world. At the present time, Marfan patients are best advised to have surgery at a medical center that has a good deal of experience with the Marfan syndrome.

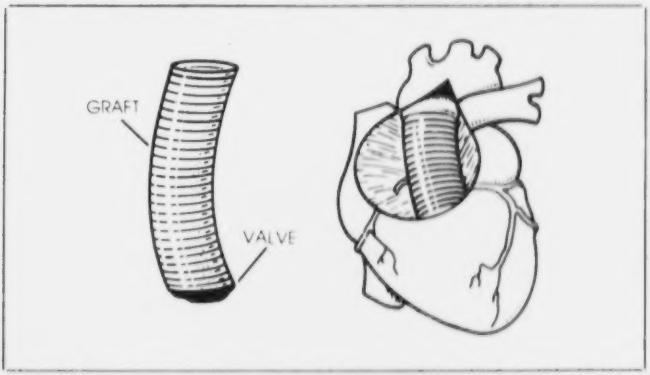

Figure 7. On the left is shown the graft with the artificial valve sewn in one end. On the right the graft is shown sewn into the aorta just before the wall of the aorta is wrapped around the graft and sewn together.

After valve replacement, a patient must take an anticoagulant medication forever. This medication (often Coumadin) reduces the chances of a blood clot forming on the prosthetic valve. Many factors, including diet, alcohol and other medications can alter the effect of Coumadin. This necessitates a periodic (about monthly) blood test and regular contact with a physician to regulate the dose and insure effective therapy.

Because of the abnormalities of the heart valves, any person affected by the Marfan syndrome is at increased risk for an infection of the valve (endocarditis). Certain procedures, such as tooth extraction or surgery on the genital and urinary systems, tend to introduce bacteria to the blood stream. Antibiotics taken just before and for two days after procedures (endocarditis prophylaxis) effectively reduce the risk. Penicillin is a satisfactory drug and erythromycin can be used by people allergic to penicillin. Adults should take 1,000 mg of penicillin orally about one hour before having their teeth cleaned or a tooth pulled, and 250 mg every six hours afterward for eight more doses. Children between 5 and 12 should take one-half of these doses. Younger children should be treated as directed by their pediatrician.

A group of medications, called beta-adrenergic blocking drugs (beta-blockers) are prescribed widely to regulate blood pressure and heart rhythm. Two of these drugs, propranolol (Inderal®) and atenolol (Tenormin®), are useful in treatment of the cardiovascular problems in the Marfan syndrome. Both drugs reduce the strength and the frequency of contraction of the heart, and in doing so, reduce strain on the aorta. Recent studies have shown that propranolol slows the rate of enlargement of the aortic root in both children and adults with the Marfan syndrome. Both medications cause few side effects and offer much promise for delaying, or possibly preventing, the need for surgery. The dosage needs to be individualized and therapy closely monitored, particularly at the beginning.

All Marfan patients should avoid lifting heavy objects, isometric exercise (straining against an immovable resistance), and exercise at maximal capacity, because of the increased strain on the aorta produced by vigorous heart action. Likewise, because the aortic wall is weaker than normal, contact sports, such as football and basketball (yes, basketball is a contact sport!) should be avoided. These guidelines often represent the most difficult aspect of management, particularly in young people and in anyone used to hard work or play. Occasionally, drastic changes in lifestyle must be made in the interests of protecting one's health. It is far easier to channel a child's interests into activities that do not require vigorous physical exertion than to tell a somewhat older child that basketball or track must

be given up. On the other hand, few young children need restrictions on their everyday activities and playing.

What Is the Outlook for Affected Persons?

The outlook is far brighter than it was even five years ago. In the days before open-heart surgery, the average life-expectancy was reduced by one-third. Medical problems, primarily involving the aorta, reduced the life span of men to about 40 years, on average, and of women to about 50 years. There was great variation about these averages, and many children died of cardiac problems. Now, early diagnosis and careful management have greatly improved the prognosis, and life-expectancy is much lengthened. Unfortunately, a small percentage of children are born with such a severe form of the Marfan syndrome that even the most advanced and aggressive therapy fails to improve their condition or prolong their life expectancy.

How Is Lifestyle Affected by the Marfan Syndrome?

Many patients believe that major life decisions, on issues such as education, occupation, marriage and children, have been little influenced by their condition. Others will state that the Marfan syndrome has been the major consideration in all such decisions. Although occupations and recreational activities that involve vigorous exertion or lifting should be avoided, the vast majority of individuals easily adapt to these restrictions. Persons affected by the Marfan syndrome hold positions of prominence in all the professions, in business and in government. Frequently, their friends, colleagues and clients are unaware of the existence of a medical condition.

What Are Some Common Reactions Of Parents?

Parents who themselves are unaffected by Marfan syndrome may still feel responsible for their child having the condition, even though this was obviously not an intentional, or even an avoidable, act. Initially, parents may feel numb and later may feel angry and sad. A parent who has Marfan syndrome may feel even more responsible, particularly if he or she had genetic counseling and was aware of the risk of a child inheriting the syndrome.

Not all parents need therapeutic counseling, but most parents do need to face their initial reactions to learning that their child has Marfan syndrome. Often a counselor, such as a social worker, psychologist, or member of the clergy with

knowledge of genetic disorders, can help parents cope with the impact of the diagnosis. Meetings with other parents who are going through, or have already experienced, similar coping stages can be extremely helpful in combating the loneliness of facing this situation. The National Marfan Foundation can be of assistance to parents, as well as to affected individuals and other family members. Occasionally, parents need professional help in dealing with their tendency to overprotect their child from hurtful experiences, a response which may prevent the child with Marfan syndrome from becoming self-sufficient and independent in later years. It is essential for the child to lead as normal a life as possible, within the physicians' limits, and to be like his or her friends.

What Are Some Common Reactions Of Affected Adults?

An adult who learns that he or she has the Marfan syndrome is usually aware of some sort of health problems already—only no label had ever been placed on the assorted problems! Other aspects of the syndrome, such as aortic enlargement, might not be discovered until the label "Marfan" is attached and specific tests, such as an echocardiogram, performed. A gloomy future may be described by a physician who is unaware of recent advances in treatment. The patient and family may feel frustrated and frightened by the perceived hopelessness of the situation and the sudden "loss of health." The genetic nature of the Marfan syndrome may involve recommendations for testing of relatives and may influence plans for having children. Adjusting to the diagnosis is *usually* associated with difficulties—social, emotional, economic and psychologic. These adjustments may, and often *should*, take place over a period of time.

It is important for the affected adult to be given correct medical information about the Marfan syndrome and to understand the need for, and benefit of, proper medical care. It is not uncommon for the affected adult to be confused or even stunned when first learning of the diagnosis, or to deny the presence of the condition. This denial can be destructive when it results in avoidance of appropriate medical care or in the continuation of activities, such as vigorous sports or occupations, that can be harmful. The National Marfan Foundation can provide support, encouragement and information to the adult who is newly diagnosed.

How Do Teenagers And Young Adults React To Being Told They Have Marfan Syndrome?

Many teenagers and young adults believe that they look dif-

ferent from others, whether or not this is based on reality. Those with the Marfan syndrome may feel particularly self-conscious about the way they look. When they are first told that they have Marfan syndrome, they sometimes feel relieved that there is a reason why they are taller than their friends, have thick glasses, a curved spine, or a chest that protrudes or indents. Often, they feel annoyed or frightened that they need to come to a clinic for regular checkups, and upset if medication is prescribed—one more intrusion into their everyday routine. They can be reassured that preventive treatment for Marfan syndrome has advanced rapidly, and continues to advance, and they can be helped to understand recommended treatment. Frequently, they are angry, particularly if they are told they must give up a competitive sport, such as basketball or running, that has been an integral part of their life. They may direct their anger at their physician, their parents (towards whom it is "safe" to vent anger), or themselves. Channeling their interests into less stressful sports, into becoming the team manager, or playing in the band may be good alternatives. Another possible avenue may be to develop other skills or talents that had been dormant.

Supportive counseling can be helpful to teenagers and young adults with Marfan syndrome. Often it is beneficial for the affected young person to talk with another person of similar age who also has the Marfan syndrome. If surgery has been recommended, it can be quite advantageous to speak with someone who has had the same or similar surgical procedure, remembering at the same time that Marfan syndrome varies considerably from person to person, even within the same family. The National Marfan Foundation or most genetic centers can be of assistance in finding the appropriate person to contact.

What Are Some Family Concerns?

A genetic diagnosis such as Marfan syndrome affects the entire family. Couples may experience a temporary strain in their relationship when they first learn that their child has Marfan syndrome. They need to communicate to each other their hopes and their fears.

Grandparents may blame themselves for their grandchild's condition, or may place the blame on "the other family." They often do not understand the diagnosis, deny the reality of it, and place faith in a reassuring acquaintance or in a miracle cure. If grandparents can be included in discussions about Marfan syndrome, they will make an easier adaptation to the diagnosis and offer potential support to the parents.

Unaffected brothers and sisters need support also. They may feel guilty that they "escaped" Marfan syndrome or fearful that they may still become affected. They may need special time with their parents to talk about their feelings, ask their questions, or gain reassurance that parents are as interested in

them as in their affected sib.

Questions that may be asked by those affected or by other members of the family include:

Why did this happen to me?

What did I do to cause this to happen?

What risk do I have of having a child with Marfan syndrome?

Is there a cure?

How will my friends, my fiance, my boss react?

What career can I choose?

Am I, like my genes, abnormal?

All of these questions are natural and normal. The answers to most appear elsewhere in this booklet. However, it is important to realize that everyone has a number of genes that are not normal, even if a physical problem does not result in most cases. A positive self-image is not dependent on one's genes!

Genetic counseling is available for each family member, and other supportive and educational counseling is also possible, for those who want it. In addition, the National Marfan Foundation offers information, resources, referrals, and support for those who are interested.

Are Medications Or Special Diets Routinely Necessary?

All Marfan patients should be considered for treatment with a beta-blocker drug, propranolol or atenolol. Either of these medications is prescribed to reduce strain on the aorta. Such therapy must be prescribed and monitored by a physician and may not be appropriate for people with diabetes, asthma or heart failure. People who have had artificial heart valves implanted require a daily medication that reduces the chance of blood clot formation on the valve. All persons with the Marfan syndrome should take an antibiotic just before and for two days after dental procedures. Occasionally, patients will need medications, such as diuretics, digoxin, hormones, and so on, for specific problems.

No specific vitamin, mineral, dietary supplement, or protein derivative is of any proven benefit. A balanced, nutritious diet, restriction of salt, cholesterol, and animal fats, and avoidance of smoking are all excellent ways of attaining, and maintaining, better health and will certainly improve anyone's ability to cope with the Marfan syndrome.

How is the Marfan Syndrome Passed in Families?

Males and females are affected by the Marfan syndrome equally frequently and with similar *average* severity. The con-

dition occurs in successive generations, with each child of an affected parent having a fifty-fifty chance of inheriting the condition, regardless of whether the affected parent is a man or a woman. Only *one* parent need be affected. In about one-quarter of all cases of the Marfan syndrome, neither parent is affected; the condition arises in the affected individual because of a spontaneous mutation in the sperm or the egg of one of the parents. In such families, the age of the father is greater, on average than that of fathers in the general population, suggesting that the spontaneous mutation occurs most often in the cells of the testes that produce sperm. Mutations occur in the germ cells constantly; the mutation that causes the Marfan syndrome arises quite infrequently, about once every 50,000 births. When neither parent of a Marfan child is affected, their risk of having another child with the Marfan syndrome is in the range of 1 in 50,000.

Although the range of severity of the condition (variable expression) can be exceedingly wide among affected relatives, few, if any, people have the Marfan gene

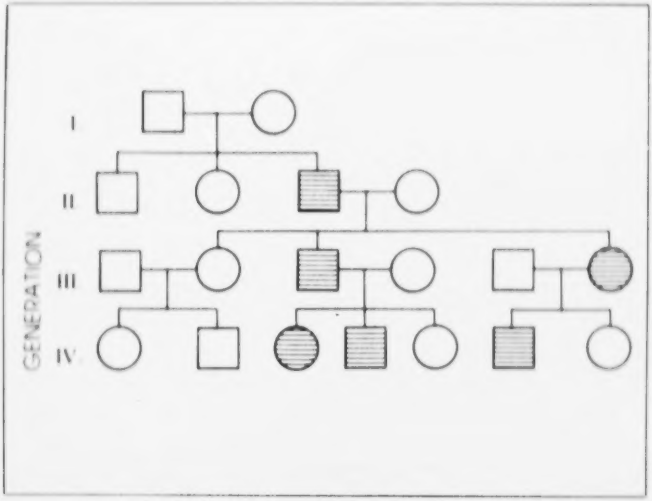

Figure 8. A Sketch of pedigree of a family in which the Marfan syndrome occurs. Squares indicate men and circles women; an open symbol means the individual was not affected with the Marfan syndrome and a shaded symbol indicates that the Marfan syndrome was present. In generation I, neither parent was affected so that the affected man in generation II must have arisen as a result of a new mutation. On average, each of children (generation III) had a 50-50 chance of inheriting the condition. When an individual does not inherit the condition, he or she has no chance of passing it on to future generations.

but fail to show some outward evidence of it. There are, therefore, no "skipped generations". If someone does not have the Marfan syndrome, then he or she cannot pass the condition to offspring.

All of these characteristics are distinctive of a specific type of inheritance, called autosomal dominant. *Autosomal* refers to the fact that the Marfan gene does not occur on one of the sex chromosomes. *Dominant* means that only one copy of the pair of genes needs to carry the Marfan mutation for the condition to be present. The alternate form of inheritance is recessive, in which both parents must carry a copy of the mutant gene, as in sickle cell disease and cystic fibrosis. Other examples of autosomal dominant conditions are familial hypercholesterolemia (one of the causes of severe elevation of blood cholesterol), neurofibromatosis ("elephant man" disease), several conditions that cause multiple polyps in the large bowel and predispose to cancer, and many of the other heritable disorders of connective tissue. Close to 2000 separate conditions and traits can be classified as autosomal dominant.

What About Having Children?

Having children is an intensely personal decision, one that should be made solely by prospective parents, but only after acknowledging and understanding potential risks to the child and the mother. *Each offspring of an affected parent has a fifty-fifty (one in two) chance of developing the Marfan syndrome.* Because of variable expression of the Marfan gene, it is not possible to predict how severely a child who inherits the gene will be affected.

Many heritable conditions can be diagnosed in unborn children by one of several techniques (ultrasound, amniocentesis). At this time, no test is available to determine if an unborn child does or does not have the Marfan gene.

Pregnancy poses additional risks to women with the Marfan syndrome because of the increased stress on the cardiovascular system. While there is no clear distinction between women who can and cannot tolerate pregnancy, several points seem established. Women who have significant heart valve problems should not attempt pregnancy. If the aorta is enlarged more than about ten percent (40 millimeters), the risk of tearing the wall of the aorta is substantial. Women are well advised to complete child bearing early in life. Any pregnancy in a woman affected by the Marfan syndrome should be considered "high-risk" (a term obstetricians use) and evaluated by echocardiography every six weeks or so. Delivery should be

by the least stressful method possible; usually this means a normal vaginal delivery. Cesarean section is not necessary on account of the Marfan syndrome, but may be indicated for any of the reasons usually applied in labor.

What Physicians Need to be Involved in Routine Medical Care?

Every person needs a physician who can be turned to for "routine" illnesses and questions. Most physicians who provide these functions know little about the Marfan syndrome or do not feel comfortable taking care of the specialized problems that Marfan patients might develop. So, in addition to a personal physician (internist, pediatrician, family practioner), it is important to have one physician who understands all aspects of the Marfan syndrome; someone who can evaluate all of the systems that might be affected, to coordinate referral to specialists when needed, and to counsel about prognosis, treatment and inheritance. Most medical geneticists can fulfill these roles. For the present, however, medical geneticists tend to be located at medical centers affiliated with medical schools. But so are many of the specialists who have the most experience with the Marfan syndrome. For most people, an annual or semiannual visit to such a physician in such a center will be all that is required to deal with the Marfan syndrome.

What Research is Being Conducted?

Both clinical and basic research are being conducted. Examples of clinical research include the study of the usefulness of beta-adrenergic blocking drugs in preventing aortic problems, a study of the extent of variable expression within large families, and a study of the frequency and extent of mitral valve problems in children. Basic research is being conducted on the cause of the Marfan syndrome, including studies of the biochemistry of connective tissue, either obtained from surgical specimens or produced by growing cells in the laboratory from small biopsy specimens, and of the location and nature of the genetic mutation itself. Nearly all of the research is being conducted by persons associated with medical schools and universities. In the United States, much of the research is supported by grants from the National Institutes of Health, although the level of support is constantly insufficient to meet the need.

Are Any Organizations Available to Provide Support and Information?

The National Marfan Foundation was chartered in 1981 by patients and physicians who had three main goals:

1. To provide accurate and timely information about this condition to patients, family members and physicians;

2. To provide means for patients and relatives to share in experiences, to support one another, and to improve their medical care; and,

3. To support and foster research.

This brochure is one outgrowth of the first goal. Additional information, particularly referral to recent scientific articles, is available on request. The Foundation can provide information about physicians experienced in the management of the Marfan syndrome.

For additional information, contact:

*National***Marfan***Foundation*

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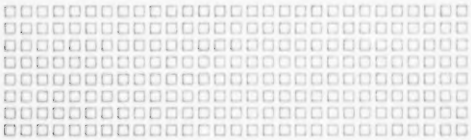
JULIA CONANT, M.D. is a graduate of Tufts University School of Medicine in Boston. She completed an internship in Pathology at the New York Hospital-Cornell Medical Center, and then practiced for one year in the U.S. Air Force. At that time she suffered an acute aortic dissection, and the diagnosis of the Marfan syndrome was made. She has undergone multiple surgical procedures related to the Marfan syndrome and its complications.

THE MARFAN SYNDROME



THE NATIONAL MARFAN FOUNDATION

FACT SHEET

WHAT IS THE MARFAN SYNDROME?

The Marfan syndrome is a heritable disorder of the connective tissue that affects many organ systems, including the skeleton, the lungs, the eyes and the heart and blood vessels. The condition can affect both men and women of any race or ethnic group. It is estimated that over 30,000 people in the United States have the Marfan syndrome.

WHAT MEDICAL PROBLEMS ARE ASSOCIATED WITH THE MARFAN SYNDROME?

The most serious problems associated with the Marfan syndrome involve the cardiovascular system. The two leaflets of the mitral valve may billow backward when the heart contracts, a condition called "mitral valve prolapse." This feature may lead to leakage of the mitral valve or be associated with irregular heart rhythm.

The aorta (the main artery carrying blood away from the heart) is generally wider and more fragile in patients with the Marfan syndrome. This widening is progressive and may result in leakage of the aortic valve or in the development of tears (dissection) in the wall of the aorta. When the aorta becomes greatly widened or torn, surgical repair is necessary.

Skeletal manifestations include curvature of the spine (scoliosis), abnormally shaped chest ("pectus" deformity), tall stature, and loose jointedness.

People with the Marfan syndrome are generally near-sighted (myopic). In addition, about half have dislocation of the ocular lens.

HOW IS THE MARFAN SYNDROME DIAGNOSED?

The Marfan syndrome may be difficult to diagnose because there is no specific laboratory test for the condition. In addition, signs of the condition vary greatly from one person to the next. Most affected people will not have all the possible signs and complications of the Marfan syndrome.

In general, the Marfan syndrome is diagnosed after a careful physical examination particularly focusing on the systems involved. Certain tests, such as the echocardiogram (a sound-wave picture of the heart) or "slit-lamp" examination by an ophthalmologist, are useful in making the diagnosis.

HOW IS THE MARFAN SYNDROME TREATED?

People affected by the Marfan syndrome should be treated by a physician familar with the condition and knowledgeable about how it affects all body systems . There is no cure for this condition yet, but careful medical management can greatly improve prognosis and lengthen life span.

Every person with the Marfan syndrome should have yearly echocardiograms to check the size and function of the heart and aorta. Each person should have an initial eye exam, with a slit-lamp to detect lens dislocations, and periodic follow-up with an ophthalmologist as necessary. The skeletal system should be carefully monitored, especially during childhood and adolescence.

A physician might prescribe a medication, called a beta-blocker, to lower blood pressure and thereby reduce stress on the aorta. People with mitral valve prolapse might need to take antibiotics around the time of dental or genito-urinary procedures to reduce the risk of infection. In order to reduce the risk of injury to the aorta, people with Marfan syndrome are advised to avoid strenuous exercise and contact sports.

WHAT CAUSES MARFAN SYNDROME?

A single abnormal (mutant) gene causes the condition. Most of the time, this gene is inherited from a parent who is also affected. About one-quarter of the cases occur when the abnormal gene arises in an egg or a sperm (a "new mutation") of an unaffected parent.

The Marfan syndrome is inherited as an "autosomal dominant" condition. This means that someone with the Marfan syndrome has a 50–50 chance that any offspring will inherit the condition.

NATIONAL MARFAN FOUNDATION

The National Marfan Foundation began in 1982 in Baltimore, Maryland. It was founded by individuals affected by the Marfan syndrome and their families. The organization is now incorporated and tax-exempt. It has expanded to include a national headquarters in Port Washington, New York, and a number of chapters across the country.

ORGANIZATIONAL GOALS

The NMF has a threefold purpose: 1) to disseminate accurate and timely information about this condition to patients, family members and physicians; 2) to provide means for patients and relatives to share experiences, support one another, and improve their medical care; 3) to support and foster research.

CHAPTERS

Since 1982 a number of chapters and informal local groups have emerged. While these groups promote the interests of the national organization, they also provide a forum for active individual participation on a regional level. Through local chapters, individuals can share experiences, provide support in critical situations, and help to alleviate the sense of alienation and aloneness that often accompanies the diagnosis of Marfan syndrome.

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ACTIVITIES

During its brief existence the National Marfan Foundation has completed a number of projects. In 1982 it published a pamphlet entitled Marfan syndrome, coauthored by Dr. Reed Pyeritz and Dr. Julia Conant. This pamphlet explains the condition in language understandable to both families and physicians, and has become an invaluable educational tool. The NMF has also published a children's story, *How John Was Unique*, which encourages children with the Marfan syndrome to develop self-awareness and self-esteem.

The NMF publishes a quarterly newsletter, called *Connective Issues*, as well as an annual report. These publications are distributed widely to institutions and a mailing list of 9,000 individuals.

The organization holds a national convention each summer that includes speakers, panels and workshops. These meetings provide an opportunity to share information among affected people and the medical profession, and have been the basis for many longlasting friendships.

The National Marfan Research Fund was established in 1986 as the research arm of the National Marfan Foundation and all funds are reserved for future research programs.

PLEASE DETACH AND RETURN

- ☐ I want to make a donation in the amount of _____.
- ☐ I would like to become a member of the NMF ($20).
- ☐ I would like to release my name to be contacted by other NMF members.
- ☐ Please send me your information packet.

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*NATIONAL***MARFAN***FOUNDATION*
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